REMARKS

Claims 1-22 are pending and are under examination. Claims 1-22 were rejected under 35 U.S.C. §112, first paragraph, claims 17-22 were rejected under 35 U.S.C. § 102(b) and claims 9-22 were rejected under 35 U.S.C. § 103.

By this submission, claim 1 has been amended, without prejudice or disclaimer of any previously claimed subject matter. Support for the amendment to claim 1 is found, *inter alia*, at page 8, line 26, to page 9, line 6, and in Example 2 at pages 44-46.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is entitled "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**".

Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Applicants have carefully considered the points raised in the Office Action and believe that the Examiner's concerns have been addressed as described herein, thereby placing this case into condition for allowance, which is respectfully requested.

Rejections under 35 U.S.C. §112, first paragraph

A. Claims 1-8 are rejected under 35 U.S.C. §112, first paragraph, as allegedly nonenabled. Applicants respectfully traverse this rejection. Applicants also note that, in the interest of expediting prosecution, claim 1 has been amended to recite a method of delaying development of a papillomavirus infection.

With regard to the rejection, as an initial matter, Applicants traverse the Examiner's assertion that "[t]he specification does not disclose the use of said ISS in preventing the symptoms of a human or animal papillomavirus" (Office Action, page 3). Such uses are disclosed, for example, on pages 19-21 of the specification, which describe, *inter alia*, "methods

for preventing one or more symptoms of papillomavirus infection" (page 19, lines 16-17) by administering "[a]n ISS-containing composition which does not include papillomavirus . . . to individuals who are infected with papillomavirus, who have been exposed to papillomavirus or who are at risk of being exposed to papillomavirus" (page 19, lines 24-27). Administration of an ISS-containing polynucleotide before onset of symptoms of papillomavirus infection is also disclosed, for example, on page 34, lines 19-21, and on page 35, lines 12-14.

Applicants respectfully point out that MPEP § 2164.01(a) lists the factors which must be considered in an enablement analysis, as set forth in *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). These factors include: (A) the breadth of the claims; (B) the nature of the invention; (C) the state of the prior art; (D) the level of one of ordinary skill; (E) the level of predictability in the art; (F) the amount of direction provided by the inventor; (G) the existence of working examples; and (H) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. The MPEP states that "[i]t is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others." The Examiner has rejected the claims based on only one of the above factors, the existence of working examples, and thus has not satisfied the legal standard for an enablement rejection.

The Examiner refers to two examples provided in the specification as a basis for the rejection of claims 1-8. The Examiner questions the results of the Examples and uses this as a basis for concluding that the specification fails to provide sufficient guidance to enable claims 1-8. As discussed above, Applicants respectfully point out that the existence of working examples is only one of several factors which must be weighed in an enablement analysis. Here, the Examiner considered only one of eight factors and appears to have ignored the other seven. The factors must all be considered in an enablement analysis; no one factor is dispositive. The Examiner discusses the working examples in the specification (factor G), but does not analyze the enablement of Applicants' invention in terms of the other factors, as required by the court's

decision in *In re Wands* and the MPEP. A rejection based on one of these factors alone, while ignoring the other factors, is improper.

Even if the examples provided in the specification did not directly address prevention of a symptom of papillomavirus, which Applicants do not admit, the existence of working examples is only one of the factors to be considered in an enablement analysis, as discussed above. The specification in its entirety provides sufficient guidance to teach one of skill in the art how to make and use the invention for prevention of symptoms of papillomavirus infection. Applicants respectfully traverse the Examiner's assertion that insufficient guidance is provided. Examples of ISS-containing polynucleotides and methods for their synthesis are provided, for example, on pages 21-29. Examples of administration regimens are provided, for example, on pages 34-35. Examples of formulations are provided, for example, on page 36. Examples of dosage ranges are provided, for example, on page 37. Examples of means of administration are provided, for example, on pages 37-39. Means for assessment of prevention of one or more symptoms of papillomavirus infection are provided, for example, on pages 39-40. Such extensive disclosure provides adequate guidance such that a skilled artisan would be able to practice the invention without undue experimentation.

With respect to the enablement requirement for patentability, the burden is on the Examiner to show that the specification is not enabling. MPEP § 2164.04 states that "[a] specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." The MPEP cites the decision in *In re Marzocchi*, 439 F.2d 220, 224 (CCPA 1971), in which the court held that the Patent Office, when making a rejection on the basis of nonenablement, must explain why it doubts the truth or accuracy of the disclosure by backing up its assertion with acceptable contrary evidence or reasoning. The Examiner has failed to meet this burden. There

is no discussion in the Office Action of the disclosure of the invention in the specification, other than the examples, and no evidence or reasoning provided that would serve to rebut the presumption that the disclosure provided in the specification is enabling.

The Examiner also states that "the unpredictability of cancer gene therapy . . . would have required a skilled artisan to engage in undue experimentation to practice the invention to prevent a symptom of papilloma infection" (Office Action, page 3). As discussed more fully below, the present invention does not encompass "cancer gene therapy." Therefore, the Examiner's statement does not apply to and is not appropriate to an analysis of the claims at issue.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

B. Claims 9-22 are rejected under 35 U.S.C. §112, first paragraph as allegedly nonenabled. Applicants respectfully traverse this rejection.

The Examiner admits that the specification is enabling for a method of reducing severity of a symptom of papillomavirus infection in dogs and rabbits, but states that the specification "does not reasonably provide enablement for a method of reducing the severity of a symptom of papillomavirus infection in any individual or mammal" (Office Action, page 4). The Examiner appears to be referring to the Examples, which disclose administration of an ISS to dogs and rabbits. As discussed above, analysis of enablement using only one of the *Wands* factors (*i.e.*, existence of working examples) is improper.[1] All eight *Wands* factors must be considered in an enablement analysis.

The specification provides adequate guidance to enable one of skill in the art to make and use the claimed invention.[2] Examples of ISS-containing polynucleotides and methods for their

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[1] The Examiner also discusses level of predictability in the art, but as discussed *infra*, the discussion relates to the art of gene therapy, rather than the art of immunostimulatory sequences, and therefore is inappropriate to an analysis of enablement of the claimed invention.

[2] Although the Examiner states that "[c]laims 9-22 are drawn to a method of reducing severity of a symptom of papilloma formation in an individual infected with papillomavirus,

synthesis are provided, for example, on pages 21-29. Examples of administration regimens are provided, for example, on pages 34-35. Examples of formulations are provided, for example, on page 36. Examples of dosage ranges are provided, for example, on page 37. Examples of means of administration are provided, for example, on pages 37-39. Means for assessment of palliation and/or improvement of one or more symptoms of papillomavirus infection are provided, for example, on pages 39-40. Examples of kits of the invention are provided on pages 41-43. Such extensive disclosure provides adequate guidance such that a skilled artisan would be able to practice the invention without undue experimentation. The burden is on the Examiner to show that the specification is not enabling (MPEP § 2164.04).

With respect to the Examiner's assertion that enablement for dogs and rabbits is insufficient to provide enablement for "any individual or mammal," Applicants respectfully point out that it is a well-established principle of patent law that "patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art." *In re Vaeck*, 947 F.2d 488, 496 (Fed. Cir. 1991). In *In re Angstadt*, the Court of Customs and Patent Appeals considered the issue of whether section 112 requires disclosure of a test with every species covered by a claim and concluded that requirement of such a complete disclosure would necessitate a patent application with thousands of examples and "would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments." *In re Angstadt*, 537 F.2d 498, 502 (CCPA 1976). The court concluded that such a requirement would be against public policy because it would have the effect of "depriving inventors of claims which adequately protect them and [would limit] them to claims which practically invite appropriation of the invention while avoiding infringement[, which would] inevitably [have] the effect of suppressing disclosure." *Id.* at 504. In conclusion, based on the foregoing, Applicants

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comprising administering a composition comprising a polynucleotide comprising an immunostimulatory sequence to said individual" (Office Action, page 4), claims 9-16 are directed to a method of reducing severity of a symptom of papillomavirus infection in an individual infected with papillomavirus, while claims 17-22 are directed to a kit for use in treatment of a symptom of papillomavirus infection in an individual infected with, exposed to or at risk of being exposed to papillomavirus.

traverse the suggestion that enablement in dogs and rabbits is insufficient to enable the invention as claimed, particularly in view of the disclosure in the specification.

MPEP §2164.02 states that an "*in vivo* animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention" and that ""[c]orrelation" as used herein refers to the relationship between *in vitro* or *in vivo* animal model assays and a disclosed or a claimed method of use." The same section of MPEP also states that "if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate." It is well known in the art, and described in the specification, for example, on page 13, that a wide variety of animals are subject to papillomavirus infection. Rabbit and canine models used in this application are art-accepted models for the study of papillomavirus infection.[3] Therefore, Applicant traverses the contention that enablement in this animal model is insufficient to enable the invention as claimed.

The Examiner further states that Dartmann et al. (*Virology* 151:124-130 (1986), "Dartmann") disclose the sequence 5'-AACGTCCG-3' as part of a human papillomavirus genome and states that the specification does not disclose the definition of the term "antigen" and therefore, the Examiner is giving the term its "broadest reasonable interpretation" and considering any nucleic acid that can stimulate the immune system to be an antigen (Office Action, page 5). Apparently equating an ISS with a papillomavirus antigen, the Examiner concludes that "claims 9, 10, 17 and 18 are not enabled for the immunostimulatory effect shown by the ISS of the instant invention in the absence of papillomavirus antigen." Applicants respectfully traverse.

Applicants disagree with the Examiner's interpretation of the term "antigen" to include "any nucleic acid that can stimulate immune system." During examination, "the words of the claim must be given their plain meaning unless applicant has provided a clear definition in the

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[3] See, for example, Sundaram et al. (*Vaccine* 16:613-623 (1998), of record), page 614, column 1; Schlegel et al. (U.S. Pat. No. 5,874,089, of record), column 2, lines 29-36.

specification." MPEP § 2111.01. The term "antigen" is well known in the art and defined, for example, as "any substance or material that is specifically recognized by antibody or a T cell receptor."[4] Immunostimulatory polynucleotide sequences are also generally known in the art and are described in the specification as polynucleotide sequences that effect measurable immune responses. Generally, ISS polynucleotides stimulate a Th1-type immune response. See specification, for example, at page 17, line 22, to page 18, line 2. ISS sequences are generally not described in the art as substances that are specifically recognized by antibodies or T cell receptors. Thus, Applicants submit that including the ISS of the present invention in the definition of antigen is beyond the "broadest reasonable interpretation" of antigen and that interpreting the ISS of the claimed invention as "an antigen of papillomavirus origin" is patently incorrect.

In the claims, the polynucleotide comprising the ISS is not the papillomavirus antigen in the claim. Further, since the claims recite "wherein *a papillomavirus antigen is not administered* in conjunction with administration of said composition" or "wherein said kit *does not comprise a papillomavirus antigen*" (emphasis added), the Examiner's point is moot. Even if, for the sake of argument, the sequence AACGTCCG were disclosed in Dartmann[5] and were antigenic, it would not be encompassed by the claims since the claims require the absence of a papillomavirus antigen.

The Examiner discusses the unpredictability of gene therapy, citing Verma et al. (*Nature* 389:239-242 (1997)), Marshall (*Science* 269:1050-1055 (1995)), and Orkin (*Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy* (Dec. 7, 1995)). Applicants respectfully submit that this basis is irrelevant with regard to the present invention, which uses immunostimulatory polynucleotide sequences. As defined in Verma et al.,

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[4] See *The Encyclopedia of Molecular Biology* (J. Kendrew, ed., 1994), page 58.

[5] As discussed more fully below, the Examiner has failed to point to the location of the sequence AACGTCCG in the long genomic sequence disclosed in Dartmann et al., and Applicants' representative has been unable to verify that this sequence is indeed part of the HPV11 genome as asserted by the Examiner.

gene therapy encompasses "putting *corrective genetic material* into cells [to alleviate] the symptoms of disease" (Verma, page 239, emphasis added). Further, Orkin defines gene therapy as a "a set of approaches to the treatment of human disease based on the transfer of *genetic material* (DNA) into an individual" (Orkin, page 3, emphasis added), discussing approaches such as "gene addition" to correct a single-gene inherited disorder, transfer of genes for cytokines as a treatment for cancer, and transfer of modified genes for viruses such as HIV as an approach to developing new vaccines (Orkin, pages 5-7). Gene therapy generally involves delivery of a transgene containing coding sequences for a gene of interest into a cell (see, *e.g.*, Verma, Fig. 1). In contrast, the present invention involves administering an immunostimulatory sequence to treat or reduce severity of a symptom of papillomavirus, rather than introduction of a gene to correct a genetic defect or to increase production of a naturally-occurring or modified protein. The Examiner's arguments with respect to the unpredictability of gene therapy are therefore moot with regard to the present invention.

The Examiner discusses Mountain (*TIBTECH* 18:119-128 (2000)) and Romano et al. (*Stem Cells* 18:19-39 (2000)) as allegedly disclosing that "naked DNA delivery results in lower delivery efficiency than vectors, brief expression in most tissues and unsuitability for targeting" (Office Action, page 6, citing Mountain) and that these limitations "make difficult the in vivo applications of nonviral gene delivery systems" (Office Action, page 6, quoting Romano et al.). The cited references discuss developments in the field of gene therapy, which as discussed above, does not relate to the present invention. For example, Mountain defines gene therapy as "the treatment or prevention of disease by gene transfer" (Mountain, page 119). The present invention does not involve transfer of a gene. The quoted passage from Romano et al. is part of a discussion of low transfection efficiency and transient transgene expression when using nonviral gene delivery systems for gene therapy applications (Romano, page 30). The present invention does not involve transgene expression. Therefore, the Examiner's arguments with respect to these references do not apply to the present invention.

The Examiner discusses Krieg (*Journal of Gene Medicine* 1:56-63 (1999)) and Tokunaga (*Jpn. J. Infect. Dis.* 52:1-11 (1999)) in the context of inflammatory responses to nucleic acids. The Examiner states that Krieg states that immunostimulatory CpG motifs "may have an unwanted effect of acute inflammatory response . . . and further suggests that the generation of immune responses is to be avoided in any *gene therapy* application" (Office Action, page 6, emphasis added). As discussed above, the present invention does not involve gene therapy, defined in Krieg as expression of an encoded gene from a vector (Krieg, page 60). Further, Krieg discusses use of current understanding of immunostimulatory and neutralizing motifs for *increasing the safety and tolerability* of gene therapy. The Examiner states that Tokunaga states that "activation of the immune system with ISS DNA could cause both beneficial as well as deleterious consequences," citing development of systemic lupus erythematosis possibly attributed to the ISS in bacterial DNA, and states that "[t]his suggests that studies in rabbits and dogs are not truly predictive of effects in other mammals and humans" (Office Action, page 7). The present claims are directed to methods and kits for reducing severity or treating a symptom of papillomavirus infection. There is no recitation in the claims regarding presence or absence of inflammation caused by the ISS. In addition, these references do not provide any support for the use of the claimed ISS resulting in these problems in the context of a papillomavirus infection. Applicants submit that the possibility of a side effect is not proper support for a lack of enablement rejection. Further, it is not necessary for Applicants to provide experimental data for every species claimed in order for the invention to be enabled, as discussed above.

The Examiner discusses Kmiec (*American Scientist* 87:240-247 (1999)) for the proposition that "animal models are not truly reflective of success in humans and are thus not predictive" (Office Action, page 7). Kmiec discusses the status of gene therapy techniques, defined in this reference as delivery to the nucleus of a cell of a correct version of a mutated gene, the expression of which will produce the normal protein and hence restore normal cellular function (Kmiec, page 241). As discussed above, the present invention does not relate to gene therapy. The claims do not involve delivery of a correct version of a mutated gene to the nucleus

of a cell to restore normal cellular function. The discussion in Kmiec with regard to animal models is not in the context of papillomavirus infection or in the use of the claimed ISS. Therefore, this reference is inapplicable to the claimed invention. Further, it is not necessary for Applicants to provide experimental data for every species claimed in order for the invention to be enabled.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under § 112, first paragraph.

Rejection under 35 U.S.C. §102

Claims 17-22 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Dartmann et al. (*Virology* 151:124-130 (1986), "Dartmann"). Applicants respectfully traverse this rejection.

In order to anticipate, a reference must disclose each and every element of a claimed invention. Claims 17-22 are directed to kits for use in treatment of a symptom of papillomavirus infection, comprising a composition comprising an ISS and instructions for use, wherein the kit does not comprise a papillomavirus antigen. Dartmann does not disclose each and every element of claims 17-22.

The Examiner alleges that Dartmann discloses "the sequence 5'-AACGTCCG-3' to be part of a human papillomavirus genome, which encompasses the limitations of claim[s] 17-22" (Office Action, page 9). As an initial matter, Applicants respectfully point out that claim 19 recites an ISS comprising a sequence selected from the group consisting of 5'-AACGTTCG-3' and 5'-GACGTTCG-3', and claim 20 recites an ISS comprising the sequence 5'-TGACTGTGAACGTTCGAGATGA-3'. None of these sequences, and hence neither claim 19 nor claim 20, are anticipated by the sequence 5'-AACGTCCG-3', which is allegedly disclosed in Dartmann. Further, Dartmann discloses a 7931 base pair nucleotide sequence of the HPV11 genome. The Examiner has failed to point out where in the 7931 base pair sequence the allegedly anticipatory sequence resides. Even if this sequence were disclosed in Dartmann,

Applicants traverse the Examiner's statement that disclosure of the sequence 5'-AACGTCCG'-3' as part of a human papillomavirus genome would encompass the limitations of claims 17-22 (Office Action, page 9).

Dartmann describes the analysis of the HPV11 genome. However, Dartmann does not disclose a composition comprising a polynucleotide comprising the claimed ISS sequence. Further, this reference does not disclose a kit comprising the composition nor a kit that does not comprise a papillomavirus antigen. Finally, Dartmann does not disclose the claimed element of instructions for administration of the composition. Accordingly, as it does not disclose each and every element of the claims, Dartmann does not anticipate the claimed invention.

The Examiner's assertion that "mere printed matter cannot impart a patentable feature to a claim" (Office Action, page 9) is incorrect. The case cited by the Examiner in support of this assertion, *In re Gulack*, 217 USPQ 401 (1983), actually reaches the opposite result.[6] In *In re Gulack*, the Federal Circuit held that "[d]ifferences between an invention and the prior art cited against it cannot be ignored merely because those differences reside in the content of the printed matter." *In re Gulack*, 703 F.2d 1381, 1384 (Fed. Cir. 1983). The *Gulack* court also referred to a previous decision by the U.S. Court of Customs and Patent Appeals which held that "[p]rinted matter may very well constitute structural limitations upon which patentability can be predicated." *In re Royka*, 490 F.2d 981, 985 (CCPA 1974). In overturning a §103 rejection by the Board of Appeals, based on the proposition that the recitation of printed matter in claims is not accorded patentable weight, the *Gulack* court stated, "the board cannot dissect a claim, excise the printed matter from it, and declare the remaining portion of the mutilated claim to be unpatentable. *The claim must be read as a whole.* If the board meant to disregard that basic principle of claim interpretation, we must reverse the rejection as a matter of law." *Gulack* at 1385 (emphasis added). The Examiner has done precisely what the *Gulack* court admonished against, by excising the printed matter from the claim and declaring the remaining portion of the

[6] The issues in *In re Gulack* were based on a 35 U.S.C. § 103 rejection. The Examiner is improperly using an obviousness case to support a 35 U.S.C. § 102(b) rejection.

claim to be unpatentable, and therefore has used an improper legal basis for rejection. The correct legal standard is a determination of whether there is a functional relationship between the printed matter and the substrate. *Gulack* at 1385. In the present claims, there is a functional relationship between instructions for administration of the composition and the composition comprising an ISS which must be administered.

Finally, the Examiner also points to the MPEP and cites *In re Casey*, 152 USPQ 235 (CCPA 1967), in support of this rejection of the kit claims. The section of the MPEP that references *In re Casey*, states that "this line of cases is limited to claims directed to machinery which works upon an article or material in its intended use. It does not apply to product claims or kit claims." MPEP § 2115.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b).

Rejection under 35 U.S.C. §103

Claims 9-22 are rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Schlegel et al. (U.S. Pat. No. 5,874,089, "Schlegel") and Sundaram et al. (*Vaccine* 16:613-623 (1998), "Sundaram"), further in view of Dartmann et al. (*Virology* 151:124-130 (1986), "Dartmann"), Krieg et al. (US Pat. No. 6,218,371) and Van Nest et al. (*39th Interscience Conference on Antimicrobial Agents and Chemotherapy*, Sept. 26-29,1999, Abstract No. 679, "Van Nest"). Applicants respectfully traverse this rejection.

A *prima facie* case for obviousness includes, *inter alia*, a requirement that references, when combined, must teach or suggest all the limitations of a claimed invention (MPEP § 2142). Here, the cited references, when combined, do not teach or suggest a method of reducing severity of a symptom of papillomavirus infection in an individual infected with papillomavirus, comprising administering a composition comprising an ISS comprising the sequence 5'-C, G, pyrimidine, pyrimidine, C, G-3', and wherein a papillomavirus antigen is not administered in conjunction with administration of the composition, as in claims 9-16, or a kit for use in

treatment of a symptom of papillomavirus infection, comprising an ISS comprising the sequence 5'-C, G, pyrimidine, pyrimidine, C, G-3' and instructions for administration, wherein the kit does not comprise a papillomavirus antigen, as in claims 17-22.

Schlegel teaches a vaccine comprising a recombinant conformationally-correct L1 capsid protein of papillomavirus, disclosed as antigenic (see, *e.g.*, column 6, line 43). Sundaram teaches a vaccine comprising the CRPV E6 gene, which encodes a papillomavirus transforming protein, and antigen-specific proliferative responses of peripheral blood mononuclear cells (PBMCs) in response to the vaccine. Neither of these references teaches or suggests a method comprising administration of an ISS, as in claims 9-16, or a kit comprising an ISS, as in claims 17-22. Both references teach a vaccine that comprises either a papillomavirus antigen or a DNA sequence that encodes a papillomavirus antigen. Since claims 9-22 require *absence of a papillomavirus antigen*, neither Schlegel nor Sundaram disclose or suggest the claimed invention in combination with any other reference.

Dartmann allegedly discloses the sequence AACGTCCG as part of a human papillomavirus genome, although, as discussed above, Applicants' representative was unable to verify this due to the length of the genome sequence disclosed and the lack of guidance from the Examiner as to the location of the cited octamer. However, even if this sequence is part of the HPV11 genome disclosed in Dartmann, this reference does not teach or suggest administration of a composition comprising a polynucleotide containing this sequence to reduce severity of a symptom of papillomavirus infection, wherein a papillomavirus antigen is not administered, as in claims 9-16, or a kit comprising a composition comprising a polynucleotide containing the sequence and instructions for administration of the composition, wherein the kit does not comprise a papillomavirus antigen, as in claims 17-22.

Krieg et al. allegedly teach the sequence AACGTTCG as an immunostimulatory sequence. Applicants respectfully traverse. Krieg et al. disclose SEQ ID NO:11, the sequence cited by the Examiner, as ATCGACTCTCGAACGTTCTC. This sequence does not satisfy the limitation of the present claims, which require the ISS to comprise the sequence 5'-C, G,

pyrimidine, pyrimidine, C, G-3'. The Examiner cites the complement to nucleotide residues 10-17 of SEQ ID NO:11 of Krieg et al. as being a disclosed immunostimulatory sequence. There is no teaching or suggestion in Krieg et al. that a complement, much less a partial complement, of a disclosed immunostimulatory sequence, could be immunostimulatory. Further, Krieg et al. teach co-administration of an ISS and a cytokine, which are disclosed as acting synergistically to produce an anti-tumor response. Krieg et al. do not teach or suggest a method or kit for treating a papillomavirus infection comprising an ISS, in the absence of a papillomavirus antigen.

Van Nest teaches co-administration of an ISS with a recombinant HBsAg vaccine to increase antibody response to the antigen of the vaccine. Van Nest does not teach administration of an ISS in the absence of antigen or kits in the absence of antigen, as in the present claims. Van Nest teaches ISS "adjuvant activity *when delivered with antigens*" (emphasis added). In addition, Van Nest does not teach or suggest anything with regard to papillomavirus or papillomavirus infection.

In conclusion, Schlegel and Sundaram teach administration of papillomavirus antigens as vaccines, and Van Nest teaches co-administration of an ISS with an antigen. Dartmann allegedly discloses that the sequence AACGTCCG is contained within a 7931 base pair HPV genome sequence but does not disclose use of the sequence for treatment of papillomavirus infection. Krieg et al. teach the sequence ATCGACTCTCGAACGTTCTC, which is not encompassed by the present claims, and does not suggest administration of an ISS in the absence of a papillomavirus antigen for treatment of papillomavirus infections. None of the references, alone or in combination, teaches or suggests a method of reducing severity of a symptom of papillomavirus infection through administration of a composition comprising an ISS-containing polynucleotide where a papillomavirus antigen is not administered in conjunction with the composition. None of the references, alone or in combination, teaches or suggests kits comprising a composition comprising an ISS-containing polynucleotide for treatment of papillomavirus infection, wherein the kit does not comprise a papillomavirus antigen. The combination of the references does not result in an invention having all of the elements of the

present claims. Therefore, these references do not render the claims unpatentable under 35 U.S.C. § 103(a).

Even if, for the sake of argument, the combination of Schlegel, Sundaram, Dartmann, Krieg et al., and Van Nest taught a method or kit with all of the same limitations as the claimed invention, there is no suggestion or motivation to modify one of the references or to combine the teachings of the five references to arrive at the claimed invention, as required for establishment of a *prima facie* case of obviousness (MPEP § 2142). None of the references teaches that it would be desirable or even possible to treat a papillomavirus infection using an ISS in the absence of a papillomavirus antigen. One of skill in the art would have no motivation to combine the five references. Applicants submit that the fact that the Examiner has combined five references indicates impermissive hindsight reconstruction for this rejection.

Lastly, a reasonable expectation of success must be provided by the modification or combination of Schlegel, Sundaram, Dartmann, Krieg et al., and Van Nest for establishment of a *prima facie* case of obviousness (MPEP § 2142). Applicants submit that as that the combination of the cited references do not suggest all of the limitations of the claimed invention, the teaching of the references would not provide one skilled in the art a reasonable expectation of success of the claimed invention.

In view of the foregoing, Applicants submit that a *prima facie* case of obviousness has not been established.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

CONCLUSION

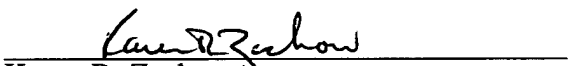
Applicants believe that all issues raised in the Office Action have been properly addressed in this response. Accordingly, reconsideration and allowance of the pending claims is respectfully requested. If it is determined that a telephone conversation would expedite the

prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 377882001300.

Respectfully submitted,

Dated: July 3, 2002

By: 

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Please enter the following amendments without prejudice or disclaimer.

In the Claims:

1. (Amended) A method [for preventing] of delaying development of a symptom of papillomavirus infection in an individual who has been exposed to papillomavirus, comprising administering a composition comprising a polynucleotide comprising an immunostimulatory sequence (ISS) to said individual, wherein the ISS comprises the sequence 5'-C, G, pyrimidine, pyrimidine, C, G-3', wherein a papillomavirus antigen is not administered in conjunction with administration of said composition, and wherein said composition is administered in an amount sufficient to [prevent] delay development of a symptom of papillomavirus infection.